REMARKS/ARGUMENTS

After entrance of the above amendments, Claims 1-5, 7-8, 10-16, 19-21, 29-30, and 32-34 are pending. Claims 23 and 25-28 were canceled, since they are directed to withdrawn subject matter as a result of a restriction requirement. Claims 17, 18, 22, 24 and 31 also have been canceled to advance prosecution in the present application (see remarks below).

Claim 1 has been amended to delete b.(i) (non-elected subject matter) and to incorporate Claims 6 and 9 therein. Claims 6 and 9 have been canceled as a result. In addition, independent Claims 21, 30, 32, 33, and 34 were similarly amended. However, such cancellations or amendments should not be construed as an abandonment of the subject matter therein or as an admission of the correctness of the Examiner's position. Applicants reserve the right to file subsequent applications directed to these claims.

Applicants have amended the Specification to include the current status of the parent application, as requested by the Examiner. Applicants also have canceled Claim 22, which was considered a duplication of Claim 21.

Claims 1-8, 10-22, 24, and 29-34 were rejected for obviousness-type double patenting over US Patent Number 6,693,086 (parent application). Note that Claim 9 was not included in this rejection and the subject matter of Claim 9 has been incorporated into Claim 1 and the other independent claims via the above amendment. Therefore, Applicants respectfully assert that the obviousness-type double patenting rejection is now moot. The claims of the '086 patent are directed to bacterially-derived nucleic acids and the present claims do not comprise a bacterial nucleic acid sequence. Thus, there cannot be double patenting.

Rejection under 35 USC §112, first paragraph

The Examiner has rejected Claims 1-22, 24, and 29-34 as being non-enabled under 35 USC §112, first paragraph. Applicants respectfully traverse, in part, and assert that the cancellation and amendment of the claims renders some aspects of the rejection moot.

Applicants have carefully reviewed the statement of the rejection and respectfully traverse because no *prima facie* case of non-enablement has been presented. As an initial matter,

the standard to apply in establishing a *prima facie* case of non-enablement is set forth in MPEP 2164.04 and by the court decisions cited therein, including the guidance provided by *In re Marzocchi* (439 F2d 220, 169 USPQ 367 (CCPA 1971)). In *Marzocchi,* the court stated:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used and describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Therefore, there is a presumption of enablement such that the burden is on the Office to provide objective reasons to defeat the presumption. Mere reliance on assertions of possibilities or conjectures is not sufficient. There must be specific reasons why undue experimentation is necessary to make and use the claimed invention.

Moreover, Applicants respectfully point out that undue experimentation is not the same as the absence of experimentation. To the contrary, the presence or need for routine and repetitive experimentation, such as provided by *In re Wands* (858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)), is entirely consistent with an enabling specification and contrary to an assertion of non-enablement.

The Specification enables the scope of the claims. On page 13 of the Specification, it is stated:

> The present inventors have made the surprising discovery that the combination of nucleic acids and liposomes is highly immunostimulatory *in vivo* when administered by intravenous or intraperitoneal injection. The potency of this immune response is far greater than the response induced by administration of either nucleic acids or liposomes alone (See Examples 1b, 1h, 2b, 12 and 13 and Figures 30 and 31), and is dependent upon the intravenous or intraperitoneal administration of the complex (See Examples 5 and 6b). Moreover, this effect is independent of whether or not a protein is encoded by or expressed by the nucleic acids (See Examples 1 and 2), and is also independent of the source of the nucleic acids, (e.g., mammalian, bacterial, insect, viral; see Examples 1g, 2c, 12 and 13), the type of nucleic acids (e.g., DNA or RNA; see Examples 7a-b), and to some extent, the type of lipids used (See Example 1f). As such, the nucleic acid-lipid complexes of the present invention induce a strong, systemic, non-antigen-specific immune response when administered intravenously or intraperitoneally,

> which results in the activation of multiple different immune effector cells *in vivo*. The present inventors have additionally discovered that the immune response generated by such a nucleic acid-lipid complex administered by the present method has potent anti-tumor, anti-allergy and anti-viral properties (See Examples 1a-c, 1h-l, 2a-d, 8 and 9).

Therefore, the Specification provides extensive support and exemplification for the scope of the present claims. In addition, Figure 6 and page 54 show that immune activation can be induced by CLDC formed with several different lipids and is not dependent on any one particular lipid composition; Figure 7 and page 55 provide that immune activation by CLDC is independent of the DNA source; and Figure 15 and page 57 demonstrate that the anti-tumor activity of CLDC (empty vector) is independent of the DNA source. Applicants respectfully submit that they have provided the required support and examples for the invention as claimed.

The Office had stated: "In addition, the specification itself teaches that at the time of filing, it was established in the art the DNA from eukaryotic sources is not stimulatory, citing a number of references, see page 55 in the specification." Applicants respectfully note that the quotation has been taken out of context and provide the text surrounding the quotation, starting on page 54:

> (g) The following experiment demonstrates that immune activation by CLDC is independent of the DNA source. It has been previously established that bacterial DNA is immunostimulatory in mammals, whereas DNA from eukaryotic sources is not …Therefore, the ability of CLDC formulated with either bacterial DNA (empty vector plasmid DNA) or eukaryotic DNA from 2 different sources (salmon sperm or calf thymus) was evaluated in vivo…Figure 7 illustrates that immune activation was observed when mice were injected with CLDC comprised of either eukaryotic or bacterial DNA.

Thus Applicants have shown a variety of types of DNA and two dramatically different types of DNA—one from a fish and one from a mammal – and an empty vector from a bacteria. Given this variability in the source, Applicants have supported their invention as claimed and have stated and shown that they successfully proceeded contrary to the then teachings in the art. The variety of experiments more than enable the claimed invention.

Contrary to the rejection, the Specification provides guidance and working examples of methods to elicit a systemic, non-antigen-specific immune response in a mammal.

Furthermore, the Huang document cited in the statement of the rejection does not support the allegation of non-enablement. Huang is only another example of what some erroneously believed prior to Applicants' invention. Furthermore, the citation by the Office of Figures 5 a-d of Huang does not support its assertion that, "Huang et al., for instance teaches that delivery of empty pcDNA vectors with liposomes fails to affect immune response associate with allergic inflammation...."

The text of Huang in this regard reads:

> To evaluate the in vivo efficacy of cytokine gene transfer in modulating allergic responses, ovalbumin-immunized A/J mice (10 μg in 200 μl volume, i.p.) were administered either 50 μl of pcDNA (5 μg vector alone) or pcDNAIFN-γ in a complex with LipofectAmine (15 μl) by aspiration four days prior to five daily aerosol challenges with ovalbumin. Twenty four hours after the last inhalational challenge, airway reactivity to i.v. acetylcholine was examined. OVA-challenged A/j mice and ARK mice which received 5 μg of pcDNAIFN displayed a significant decrease in the number and percentage of eosinophils in the bronchoalveolar lavages (BAL) as shown in FIGS. 5A and 5C. Allergen treatment of A/J and AKR mice (sensitization and challenge with conalbumin) also induced marked increases in airway reactivity compared with PBS-sensitized and challenged controls (FIGS. 5B and 5D). Administration of the mock plasmid had no significant effect on airway responses of antigen-treated mice. Strikingly, IFN-γ transgene administration to antigen-treated mice completely ablated the development of airway hyperresponsiveness. Delivery of the pcDNAIFN-γ alone resulted in significant suppression of airway hyperresponsiveness, however, the use of liposomes greatly increased the efficacy of this suppression. These data are evidence that mucosal gene transfer can inhibit allergen-induced airway hyperreactivity.

Thus Huang presents a different delivery system and different timing of delivery than Applicants. Moreover, in some instances in Huang, the combination of liposome and pcDNA did reduce the eosinophils. See Figure 5d.

In light of the above, Applicants respectfully submit that no *prima facie* case of non-enablement has been presented and moreover, even if one had, Applicants have clearly overcome it. Therefore, the rejection should be withdrawn.

Rejection under 35 USC §112, second paragraph

Claims 17 and 18 were rejected as allegedly indefinite under 35 USC §112, second paragraph, due to the inclusion of a nucleic acid sequence encoding a cytokine in these claims even though Claim 1 did not have a gene insert. Applicants have canceled these claims, thereby rendering this rejection moot.

Rejection under 35 USC §103(a)

Claims 1, 17 and 18 were rejected as obvious over US Patent Number 6,121,247 (Huang) in view of US Patent Number 5,830,878 (Gorman). Applicants respectfully traverse as to Claim 1, assuming it is still rejected after the cancellation of Claims 17 and 18.

On page 7 of the Office Action, it is stated:

> Although, claim 1 recites a vector without a gene insert, claims 17-18 which depend on claim 1 recite that the composition further comprises a nucleic acid encoding a cytokine. As indicated in the above discussion of claims 17-18 under 35 U.S.C. 112, second paragraph, it is unclear whether the nucleic acid encoding the cytokine is part of the vector or separate. As such, in the interests of compact prosecution, the following rejection applies to the embodiment of claims 17-18 which appears to encompass a single vector encoding a cytokine.

Since Applicants are no longer claiming the cytokine as stated in Claims 17 and 18, they believe that the rejection is now rendered moot and that Claim 1 will no longer be rejected in view of Huang and Gorman. Please note that Claim 1 does not include a gene insert and therefore does not include interferon gamma as shown in Huang. As a result, the obviousness rejection should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6108.

Respectfully submitted,

Karen Babyak Dow

Karen B. Dow
Reg. No. 29,684

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 858-350-6100
Fax: 415-576-0300

Attachments
KBD:ps
60988779 v1